REMARKS

Claims 1-15 and 22-36 constitute the pending claims in the present application. Applicants have added new claims 33-36. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note with appreciation the acknowledgement of the amendment filed 25 February 2002, and the withdrawal of the finality of the previous office action.

2. Applicants note that the rejection of claims 16 and 17 under 35 U.S.C. 112, second paragraph, is withdrawn in response to cancellation of claims 16 and 17.

3. Applicants note with appreciation the withdrawal of the rejection of claims 22 and 23 under 35 U.S.C. 112, first paragraph.

4-5. Claims 1, 3, 5, 25 and 26 are rejected under 35 U.S.C. 102(a) as being anticipated by Fujita et al. Applicants traverse this rejection to the extent it is maintained over the amended claims.

The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1978). "The identical invention must be shown in as complete detail as is contained in the claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Fujita et al. fail to teach a method for inhibiting proliferation and growth of lung cancer cells *in vivo*, as required by the claims. This point is explicitly noted by the Examiner in section 7 of the Office action which states that "Fujita et al. teaches as set forth above but fails to teach

in vivo use." Accordingly, Fujita et al. fail to satisfy the criteria for anticipating the claimed subject matter. Reconsideration and withdrawal of this rejection is respectfully requested.

6-7. Claims 2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujita et al. Applicants traverse this rejection.

MPEP 2142 sets forth the three basic criteria that must be met in order to establish a prima facie case of obviousness. The three criteria are that there must be some motivation to either modify the prior art reference to arrive at Applicants' invention or to combine two prior art references in order to arrive at Applicants' invention, the prior art reference or references must teach each and every limitation of the claimed invention, and there must be a reasonable expectation of success. Applicants contend that the teachings of Fujita et al. fail to satisfy all three of these criteria, and accordingly fail to render obvious the claimed invention.

The Office Action alleges that although Fujita et al. fail to teach *in vivo* methods for inhibiting tumor growth using a hedgehog antibody, it would have been obvious to one of skill in the art to use such compositions *in vivo*. Applicants concede that it may have been obvious to **try** to use hedgehog antibodies *in vivo*, however obvious to try is an insufficient basis upon which to reject the present invention under 35 U.S.C. 103(a). The Examiner has presented no evidence that given the results presented by Fujita et al. in lung cancer cell lines, one of skill in the art would have a reasonable expectation of success in using these compositions to inhibit tumor growth *in vivo*. The question is not whether one of skill would be motivated to conduct the experiments required to address this question, but whether one of skill in the art would have a reasonable expectation that such compounds could be used *in vivo* based solely on the teachings of Fujita et al. Applicants contend that this is not the case.

Furthermore, as outlined briefly above, to establish a prima facie case of obviousness, a prior art reference must teach each and every limitation of the claimed subject matter. Fujita et al. fail to teach *in vivo* treatment of lung cancer using hedgehog antibodies, or other hedgehog antagonists, as specifically required by the pending claims. Accordingly, Fujita et al. fail to teach each and every limitation of the pending claims.

The standards for establishing obviousness are clearly delineated by the MPEP. Fujita et al. fail to teach each and every limitation of the pending claims. Furthermore, although it may have been obvious to try to extend the analysis of Fujita et al. to cells and tumors *in vivo*, obvious to try is insufficient to render the claimed invention obvious. Absent a reasonable expectation of success, the claims directed to *in vivo* treatment of lung cancer tumors are not obvious in light of the teachings of Fujita et al. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 103(a).

8. Claims 22, 23, 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fujita et al., and further in view of US Patent 6261786. Applicants traverse this rejection to the extent it is maintained in light of the amended claims.

As outlined in detail above, Fujita et al. fail to teach *in vivo* application of a hedgehog antagonist to lung cancer cells, as recited by the pending claims. Accordingly, Fujita et al. fail to teach each and every limitation of the pending claims. This deficiency of Fujita et al. is not overcome by U.S. Patent 6261786. Accordingly the cited references, either individually or when considered together, fail to teach each and every limitation of the pending claims. Reconsideration and withdrawal of this rejection is respectfully requested.

9. Claims 6-15, 24 and 29-32 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants traverse this rejection.

It is a commonly understood principle of genetics that mutations or variations of a protein may result in a range of phenotypes including loss-of-function, gain-of-function, or a new function. Identification of a variant possessing one of these characteristics is in no way suggestive that mutations which will result in other characteristics do not exist. This is the central tenet of genetic analysis. If an example of a variant possessing a certain characteristic was in any way predictive that variants possessing alternative traits did not exist, there would be no purpose in conducting large-scale mutant screens as is routinely practiced by scientists experimenting with Drosophila, C. elegans, and mice. Accordingly, Applicants contend that the

reasoning underlying this rejection is inconsistent with methods which are routinely practiced in the art and which form the foundation of modern genetics.

In further support of the enablement of the claims, Applicants point out several articles which demonstrate that hedgehog variants which can antagonize the function of hedgehog exist, as would be expected by one of skill in the art. Katsuura et al. demonstrate that the deletion of approximately 9-10 amino acids from the N-terminus of Sonic hedgehog result in loss of hedgehog activity, as assayed by the ability of Sonic hedgehog to induce alkaline phosphatase in C3H10T ½ cells (Katsuura et al., 1999, enclosed herewith as Exhibit 1). The N-terminally truncated form of Sonic hedgehog does not merely represent a loss-of-function of the hedgehog protein, but can also act as an antagonist of wild type hedgehog signaling. "There was no activity even with 6000 ng/ml of desN-Shh-N and desN-Shh-N inhibited the ALPase-inducing activity by L-Shh-N in a dose-dependent manner (Fig. 4)." (Katsuura et al., page 327, column 2).

Additionally, the role of hedgehog proteins in a variety of human developmental defects is being dissected. For example, holoprosencephaly is a complex, multi-system syndrome, and heterozygous mutations in Sonic hedgehog are involved in some cases of holoprosencephaly (Orioli et al., 2001; Nanni et al., 2001, enclosed herewith as Exhibits 2-3). Although additional studies are necessary to confirm the mechanisms by which the various mutations associated with this condition cause the associated phenotypes, the large number of mutations identified in affected families, as well as the tremendous range of phenotypes among affected families suggests that multiple mechanisms may be involved. The possibility that one mechanism by which a mutation in a hedgehog protein affects development is by antagonizing wild type function is not without precedent. Mutations in Indian hedgehog result in brachydactyly type A-1 (Gao et al., 2001, enclosed herewith as Exhibit 4). One of the primary candidates for a mechanism connecting this mutation in Indian hedgehog to this disorder is that "Glu95→Lys, Asp100→Glu or Glu131→Lys effect aberrant signaling by interfering with SHH binding to its 'natural' receptor(s), or promoting its binding with other receptors." (Gao et al., page 387, column 2).

Applicants contend that based on the specification, the state of the art in genetics and development, and recent studies on the genetic basis of human disease, the claimed invention is

enabled throughout its scope. Applicants have provided extensive discussion and description of N-terminal variants of hedgehog proteins which can antagonize hedgehog function. Additionally, Applicants have provided a specific example (Exhibit 1) which demonstrates that, as outlined by the specification, one of skill in the art could reasonably expect to identify a hedgehog variant which meets the limitations of the pending claims. Exhibit 1 demonstrates that not only would one of skill in the art have expected to identify such a hedgehog variant, but in fact, one of skill in the art **did** identify such a variant. Accordingly, Applicants contend that the claims are enabled throughout their scope. Reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this Reply, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

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